individual optical isomers of that mixture. Second, she argues that such teaching amounts to an express disclosure of the claimed (-)-enantiomer. Accordingly, she concludes that the art constitutes an anticipation of the claimed subject matter.

Applicants traverse.

Applicants agree that EP-382,526 and United States patent 5,047,407 recite racemic mixtures and disclose the existence of the individual optical isomers of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane. Applicants also agree that separation of these individual enantiomers from the racemic mixture was within the skill of the art at the filing date of the instant application. However, applicants totally disagree that the claimed (-)-enantiomer was expressly disclosed in the prior art. Without such disclosure, there can be no anticipation and the § 102 rejection must fall.*

EP-382,526 and United States patent 5,047,407 identify a genus which includes the geometric and optical isomers of 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane and mixtures of those isomers. Neither specifically identifies the claimed (-)-enantiomer or its special and unexpected properties. At best, the individual optical isomers of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane are disclosed in a generic fashion as "separate optical isomers" -- i.e., either the (+) or the (-)-enantiomer.

A rejection for anticipation under § 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. In re Paulsen, 30 F.3d 1475, 1478-79 (Fed.Cir. 1994); Scripps Clinic & Res. Found. v. Genentech, Inc., 927 F.2d 1565 (Fed.Cir. 1991). Neither

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* The § 103 rejection falls because of the (-)-enantiomer possesses special and unexpected properties (infra, pp. 3-6).

EP-382,526 nor United States patent 5,047,407 satisfy this standard. Neither document describes or identifies the claimed species -- the (-)-enantiomer of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane -- other than as part of a genus. That is just not enough to anticipate a species.

The Examiner does not challenge this legal standard. Instead, she attempts to distinguish Brenner v. Ladd, In re Kaplan, and Rohm and Haas Co. v. Mobil Oil Corp. from the present situation by stating that in those cases, the prior art did not expressly disclose the claimed species. Her distinction is at odds with the facts of this case. Here, just like in Brenner, Kaplan and Rohm and Haas, the art does not expressly disclose the claimed species. As demonstrated above, a bare reference to "separate optical isomers" is not an "express disclosure" of the (-)-enantiomer of the instant invention. Thus, the authorities are on all fours with the facts here. So should the legal conclusion -- the claims are novel over the art.

With respect to the § 103 rejection, the Examiner argues that the Declaration of Richard Storer is not persuasive. In her view, it does not provide evidence that the claimed enantiomer possesses a property not possessed by the racemate or the (+)-enantiomer. Again the Examiner is absolutely mistaken.

As evidenced in the specification itself at pages 27-29, the claimed (-)-enantiomer possesses significant antiviral activity and significantly reduced cytotoxicity, thereby providing a superior therapeutic index not possessed by either the racemate or the (+)-enantiomer. Dr. Storer's Declaration demonstrates that this superior therapeutic index was surprising and unexpected.

The Examiner further argues that the significantly lower toxicity profile of the (-)-enantiomer would have been obvious in view of the "basic underlying principles of stereochemistry and what is well known by those skilled in the art regarding the likelihood of expected differences in physiological activities between two enantiomers of a given racemic pair." This is not so. The Examiner has misconstrued the evidence.

Certainly, those of skill in the art expect to see differences in physiological activities between two enantiomers. However, contrary to that expectation, the (+) and (-)-enantiomers of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane possess almost equal activity antiviral activity. And, even if one of skill in the art would have expected one of the enantiomers to be less toxic, that skilled artisan would not have predicted that the less toxic compound would also possess potent antiviral activity and thus, the surprisingly superior therapeutic index of the claimed (-)-enantiomer. Typically, activity and toxicity go hand in hand. Here, toxicity does not follow activity.

The Examiner attempts to distinguish In re Jones from the facts here by stating that the prior art in that case did not provide one skilled in the art with the motivation to make Jones' claimed compound.* The Examiner has once again incorrectly interpreted the evidence.

The Declaration of Dr. Storer demonstrates that one of skill in the art would not have been motivated to evaluate the (-)-enantiomer of *cis*-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-

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* The Examiner again asserts that applicants' claimed (-)-enantiomer was "expressly disclosed" in EP-382,526 and United States patent 5,047,407. As stated above, neither EP-382,526 nor United States patent 5,047,407 expressly discloses the claimed (-)-enantiomer.

oxathiolane. The skilled worker would have expected the anti-viral activity to reside in the natural enantiomer. Dr. Storer also testified that no one would have predicted that the claimed (-)-enantiomer would possess advantageous properties. This evidence is supported by numerous scientific publications. See, e.g., Beach et al., "Synthesis Of Enantiomerically Pure (2'R,5'S)-(-)-1-[2-(Hydroxymethyl) oxathiolan-5-yl]cytosine As A Potent Antiviral Agent Against Hepatitis B Virus (HBV) And Human Immunodeficiency Virus (HIV)", J. Org. Chem., 57, pp. 2217-2219 (1992).* Beach states that "the ß-D-isomer of nucleosides are in general the biologically active isomers" (page 2217, column 1) but concludes that "(2'R,5'S)-(-)-BCH-189 **3** [is] more potent than (2'S,5'R)-(+)-BCH-189 **2** by at least one order of magnitude. The significance of this finding is the fact that this is the first example of an L-like nucleoside found to be more potent than a D-like nucleoside" (page 2219, column 2).

Similarly, Chang et al., "Deoxycytidine Deaminase-Resistant Stereoisomer Is The Active Form Of (±)-2',3'-Dideoxy-3'-Thiacytidine In The Inhibition Of Hepatitis B Virus Replication", J. Biol. Chem., 276, pp. 13938-13942 (1992)* independently studied antiviral activities of the enantiomerically enriched 1,3-oxathiolane nucleoside analogues of this invention. Chang acknowledges that "[i]t has always been assumed that the active stereoisomer of these analogs would be the one which most closely mimicked the natural nucleoside" (page 13941, column 2). Chang also confirms that "[t]his is the first nucleoside analog with the unnatural sugar configuration demonstrated to have antiviral activity" (abstract, page 13938).

See also, the independent report of R. F. Schinazi et al., "Activities Of The Four Optical Isomers Of 2',3'-

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* Copy enclosed with July 1993 Response.

Dideoxy-3'-Thiacytidine (BCH-189) Against Human Immunodeficiency Virus Type 1 In Human Lymphocytes", Antimicrobial Agents And Chemotherapy, 36(3), pp. 672-676 (1992)* -- "[t]he unexpected finding that certain L isomers of nucleoside analogs of BCH-189 are potent and selective antiviral agents opens new approaches for the treatment of viral infections with nucleosides with the unusual L conformation [sic]."

Accordingly, the Examiner's rejection under 35 U.S.C. §§ 102 and 103 over European patent publication 382,526 ("EP-382,526") and United States patent 5,047,407 should be withdrawn.

The Examiner also contends that there is no evidence of record or available in the art to teach how to use the claimed compound for treatment of viral infection. That contention is totally without merit.

Applicants have taught that the claimed compounds are effective in inhibiting the replication of retroviruses, including HIV (specification page 3, lines 32-37). Applicant has provided information about suitable dosage (page 5), route of administration (pages 5-8), pharmaceutical formulations (pages 5-8 and Examples 6-9), combination therapies, (page 8) and biological activity (pages 27-29). Based on this disclosure, one of skill in the art of clinical medicine would certainly know how to use the claimed compounds for the asserted utility.

However, to remove any doubts that the Examiner may have, applicants submit concurrently herewith a Declaration by Dr. Hugh McDade. In his declaration, Dr. McDade demonstrates that one of skill in the art would "know how to use" the claimed invention for the asserted utility. In view of this evidence,

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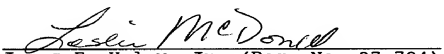
* Copy enclosed with July 1993 Response.

applicants request the Examiner to withdraw the rejection under 35 U.S.C. § 112, first paragraph.

For all of the foregoing reasons, applicants believe that the claims are in condition for allowance and request that the Examiner withdraw all rejections and allow this application.

Respectfully submitted,



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